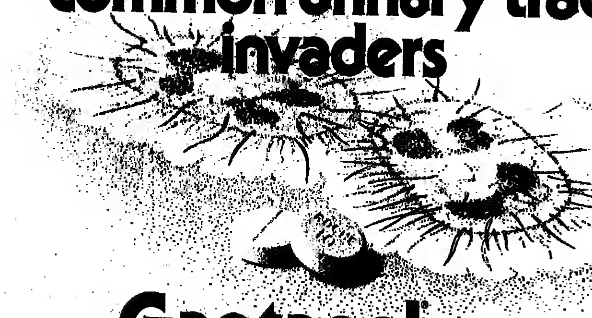
first line of offense against common urinary tract invaders



Gantanol® B.I.D.
(sulfamethoxazole)

Basic therapy in nonobstructed cystitis*

- Because it is active against susceptible strains of *E. coli* and other organisms
- Because it is effective in nonobstructed urinary tract infections such as cystitis, pyelonephritis and pyelitis
- Because it has high patient acceptance with convenient B.I.D. dosage
- Because it is economical
- Because it is available in two convenient dosage forms—tablets and suspension

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms.

Note: **Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* ... thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs b.i.d. Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

*due to susceptible organisms such as *E. coli* ... *Staph. aureus, Proteus mirabilis*, and ...

Roche Inc.

ABCD

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Med Trib 9

Medical Tribune

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and Medical News

Vol. 16, No. 9 — *world news of medicine and its practice—fast, accurate, complete* — Wednesday, March 5, 1975

Economic Shifts Spur Demand for Curbs on 'Blues'

By Linda Murray

Special Tribune Correspondent

Criticism of Blue Cross and Blue Shield for not doing their part to keep the lid on skyrocketing health care costs is nothing new. But inflation, the removal of Federal controls, and the scrutiny of a Congress none too eager to hand the plum of national health insurance to private industry, have given the long-standing dissatisfaction a new urgency.

The key issues: To what extent should and can the Blues regulate health care costs, and who should regulate the Blues?

With few exceptions, regulation by state insurance commissioners—charged with the responsibility in most states—hasn't proved particularly successful, partly because of the almost whimsical nature of state laws. In some states, proposed increases in Blue Cross and Blue Shield subscriber rates must be approved by the com-

Continued on page 2

Editorial

The Crisis at the Pasteur Institute

"If the Institute had earned royalties on the vaccines it produced, there wouldn't be any financial problem." Jacques Monod, Nobel laureate, director, Pasteur Institute.

The Pasteur Institute is the idealized prototype of the research and health service organization which consumer advocates and government regulation and legislation aim for. It is non-profit and managed by scientists; it takes out no patents to protect its discoveries; it uses no trademarks to improve its income. Today, the future of the Pasteur Institute, unique in its record of achievements in biology and health services, is bleak. Despite its epochal contributions to immunology and genetic medicine, its ability to continue to provide both therapeutic vaccines and basic research is in question. Despite the absence of a profit motive, and the efforts of a staff of over 1,000 including eight Nobel laureates dedicated to science, survival of the Pasteur Institute and the fulfillment of its basic missions are in jeopardy.

If this be true of the Pasteur Institute, can lesser organizations fare bet-

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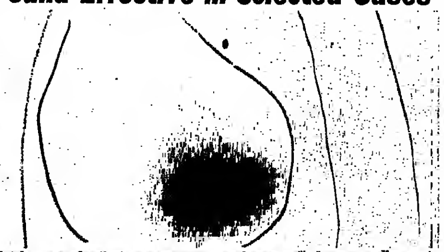
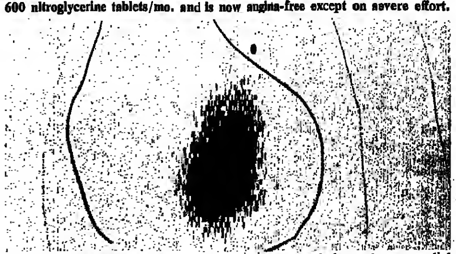
Bypass Grafts to Coronary Veins Found Effective in Selected Cases



Uptake scans of patient with saphenous vein bypass grafts from ascending aorta to anterior (I^{131} scan, above) and posterior (Tc^{99} scan, below) descending cardiac veins. Preop angiograms showed, despite previous double Vineberg and triple bypass artery procedures, occlusions of rt. and desc. coronary arteries and severe stenoses of diagonal and circumflex coronaries; patient was taking 150-600 nitroglycerine tablets/mo. and is now angina-free except on severe effort.



By Thomas Bulger

Medical Tribune World Service

Montreal—Bypass grafts to coronary veins, rather than arteries, may be an effective means of myocardial revascularization in selected cases, the Society of Thoracic Surgeons was told here.

The technique is intended to effect retrograde perfusion of myocardial capillary beds—that is, from the venous rather than the arterial side—when the arterial tree is too stenosed or occluded to be effective.

Dr. James S. Benedict, of St. Mary Medical Center, Long Beach, Calif., reported on the experience of three

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making rounds at press time

INVOLUNTARY COMMITMENT - of the mentally ill is being challenged in Iowa by Justice Department. Federal lawyers will argue that Dorothy Stemus was deprived of constitutional rights when she was kept against her will in the state institution at Clarinda. Suit charges Iowa laws discriminate against mentally ill by denying hearings and expert assistance. "We hope to win, and expose one of the worst situations in the country," said Claudia Morrissey, Executive Director of Iowa Civil Liberties Union, assisting the government. Lorna Williams, Special Assistant to Iowa Attorney General, told MT that laws in question were constitutional and state would fight suit.

WOMEN - For the first time in its 17 years, the Chicago Alcoholic Treatment Center will admit women as inpatients, following completion of a new 22-bed unit.

Identification Of Meningitis Type Speeded

Medical Tribune Report

New Orleans — Counter-immunoelectrophoresis has been shown in a study in the pediatric contagion service at the Charity Hospital in New Orleans to provide a rapid and reasonably-accurate identification of the etiology of bacterial meningitis.

It is specific, but is less sensitive than culture, and therefore is useful only when positive, according to the investigators, who noted that the procedure may be of aid in establishing the etiologic diagnosis of partially-treated meningitis.

These results were reported to the Southern Society for Pediatric Research by Dr. George M. Converse, who made the study with Dr. J. Owen Hendley.

24 Hours for Culture Results

Dr. Converse noted that the establishment of the etiology of meningitis is a frequent clinical problem; that culture is the surest method but results may not be known for 24 hours; that cultures may be negative in partially-treated cases.

In the test, cerebrospinal fluid is run against antisera to commonly encountered organisms. Dr. Converse said there is an advantage in the fact that CIEP is more rapid than culture, "but disadvantages include the possibility of cross reactions and the need for specially prepared antisera for maximum sensitivity." He suggested the test is of practical value as a procedure for augmenting present methods.

Eighty-one patients with meningitis and 45 controls were used in the study. Forty patients over two months of age were demonstrated to have acute bacterial meningitis based on the isolation of pathogenic organism from the CSF. Hemophilus influenzae was recovered from 27, meningococcus from eight and pneumococcus from five.

Eight children with aseptic (presumably viral) meningitis were studied. They had negative CSF cultures and no prior antibiotic treatment. Six patients less than two months of age had neonatal meningitis, and three had pleocytosis secondary to intracranial infection or hemorrhage.

The 45 control patients had undergone lumbar puncture for fever of unknown origin, febrile seizures or suspected meningitis. All had normal spinal fluid findings.

Twenty-four meningitis patients who received low dose antibiotics during the 48-hour period prior to

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Economic Shifts Spur Demand for Controls on 'Blue' Plans

Continued from page 1

missioner. In other states, the commissioner has standing authority to review subscriber rates. In still other states, statutes authorize the commission to review contracts between Blue Cross and the hospitals, but don't spell out how these evaluations should be made.

"Even where statutory authority to examine hospital reimbursement rates exists," points out attorney Sylvia Law, principal author of *Blue Cross: What Went Wrong?*, produced by the Health Law Project of the University of Pennsylvania, "Insurance commissioners in most states do not scrutinize them. The official position of the National Association of Insurance Commissioners is that rising hospital costs should be controlled by direct regulation of hospitals rather than through the health insurance industry."

In the absence of compelling legislation and trade-association support, the rare commissioner who decides to take on the Blues must have a little of tilting at windmills and be prepared to lay his political life on the line. No commissioner has demonstrated so dramatically the potential of Blue Cross reform by virtue of his office than Herbert S. Denenberg, Ph.D., former Insurance Commissioner of Pennsylvania, and called by some the Ralph Nader of the health insurance industry.

DR. DENENBERG

In 1971, Dr. Denenberg used his authorization to review rate increases to order five Blue Cross Plans to renegotiate hospital contracts compelling institutions to accept guidelines including consumer participation in decision-making, budgetary review, elimination of duplicated facilities and enforcement of "prudent purchasing practices."

As a result, Philadelphia Blue Cross reported a 7.8 per cent rate of inflation in local hospital costs for 1973 compared with 13.9 per cent nationally, and savings of $55 million a year which Dr. Denenberg thinks is a conservative estimate.

"Any progress made here," Dr. Denenberg comments today, "was because of intense public pressure and intense pressure from Blue Cross. Blue Cross basically had sound ideas and knew what had to be done but couldn't get the hospitals to move. Traditionally and historically, the Blues are very close to the hospitals, and this required an adversary plan. So we mobilized broad public support."

When Dr. Denenberg went after Blue Shield, he was considerably less successful. Usually, when a commissioner decides to exercise his authority, he moves against Blue Cross with its higher premiums, and reimbursements concentrated in payments to 10,000 institutions while Blue Shield's payments are scattered among nearly 200,000 doctors. Also, it is generally agreed that Blue Cross has more leverage since most hospitals depend on the carrier for a substantial portion of their income. With Blue Shield, physicians are much more likely to simply resign if the commissioner decides to get tough.

Dr. Denenberg, however, gave Blue Shield the same attention as Blue Cross and feels that is appropriate. In fact, he argues, "it may be better to go after Blue Shield because it's controlled by doctors, and you can't affect any basic reform if you don't get to the doctors."

Blue Shield in Philadelphia eventually adopted some reforms including subscribers on the Board (state law requires a majority of doctors), an experiment to pay physicians a flat rate per case based on discharge diagnosis for such conditions as pneumonia and gastroenteritis and an experiment to reimburse physicians assistants for 25 per cent less than what a physician would receive for certain procedures. But the Blue Shield moves have been much slower and are a far cry from Dr. Denenberg's original demands that participating physicians be required to take postgraduate courses, that quality controls be instituted for surgeons who don't operate often, and that there be strict monitoring of physicians' fee schedules.

Will Dr. Deanberg's example be applied elsewhere? "A lot of people have tried to copy what we've done," the originator observes. "You can get into a lot of trouble if you do."

West Virginia Situation

One of those who has been burned is West Virginia Insurance Commissioner Samuel Weese, also chairman of the subcommittee on health insurance for the National Association of Insurance Commissioners. When Commissioner Weese disapproved an increase of 34 per cent two years ago, the carrier took the insurance department to court and won. Now the case is on appeal in the state supreme court.

"It's our contention," Mr. Weese explains, "that there's no end to these increases and by approving them we would just be perpetuating a bad situation. But the real question is the scope of our authority in reviewing rate filings. Do we have the authority to go beyond the mere fact that 2 plus 2 is 4, and ask why that number is 27 Do we have the authority to approve or disapprove the hospital reimbursement rate? It's our contention that it's just a contractual arrangement, not in the best interest of the subscriber. There's no requirement for accountability, no cost control mechanism, no utilization review. We think Blue Cross might as well recognize they're in a new ballgame."

Blue Cross sees things differently. "Insurance commissioners wield powers I consider excessive and beyond statutory authority," counters C. J. Pearson, president of Blue Cross and Blue Shield in Charleston, West Virginia. Beyond assuring solvency, Mr. Pearson thinks the commissioner should have no say over the Blues, believing comoetition is the most appropriate regulatory mechanism.

But Mr. Pearson thinks that the commissioner's actions may help the Blues solve their problems trying to regulate area hospitals. "Under our statutes," he explains, "if Blue Cross gets to the point where there is a deficit in funds, the hospitals have to take a discount. We're going to let this keep going until we run out of reserves and just let the hospitals squirm. Actually, we've been fighting the hospitals' battle for years. It's about time they stepped into the picture."

The Charleston Plan has been unable to fight its own battle because it insures such a small segment of the population—about 35 per cent, up from 20 per cent four years ago, whereas in Philadelphia, the carrier writes 70 per cent of the business.

A lot of the Blues' clout also depends, Dr. Denenberg thinks, on how strong the plan is. "You can do a lot of things in Philadelphia, you can't do in Lehigh," he observes. "The Philadelphia plan is headed by a tough guy who's very capable. There was no problem putting pressure on him to pressure the hospitals. We had sound, tough management, tremendous market penetration, and public opinion on our side. If you try to do it in another area, the hospitals may just tell you to go to hell."

But even in Philadelphia, a united hospital front brandishes considerable might. When Blue Cross put the heat on metropolitan hospitals in March 1973 to sign new contracts with an 11 per cent ceiling on costs, with the exclusion of such inflationary items as food and fuel (the ceiling is required by the commissioner), 35 nonprofit hospitals steadfastly refused to sign.

"The big issue is regulation," declares Joseph A. Williamson, president of the Delaware Valley Hospital Council, which represents the dissident hospitals. "We object to control by an insurance company. We have enough in terms of cost controls. Why give them voluntarily to an insurance carrier? There is neither the legal authority nor a demonstrated need for Blue Cross to insist on regulating the independent management of hospitals."

Pressing their point, the 35 hospitals have joined with 65 others in a class action suit charging Blue Cross with violation of both the "restraint of trade" and "monopoly and conspiracy" provisions of federal antitrust laws because, they claim Blue Cross as provider of 70 per cent of all health insurance in metropolitan Philadelphia has used that position of virtual monopoly to coerce hospitals into contracts under which they have been providing their services to subscribers at a loss, made up by charging other patients more than their fair share.

Heavy Damages at Issue

If the charges are proved, Philadelphia Blue Cross would owe hospitals so much money—damages run into many millions of dollars—that it might be forced into bankruptcy. Since the hospitals also charged that the Philadelphia plan has conspired with the nation's 73 other Blue Cross plans to promote the contracts which restrain trade, conceivably every plan in the country could face such a suit.

Dr. Denenberg is putting his money on the carrier. "Blue Cross is stronger than ever," he says, "Back in '71, it was Blue Cross that was the culprit. Now it's the hospitals that are the culprits while Blue Cross is the friend of the consumer."

But in most plans, the consumer has little voice in policy-making for the Blues. Public representation on Blue Shield boards averages 39 per cent while Blue Cross reports 58 per cent and 68 per cent if one includes the hospital trustee, who can't exactly be devoid of provider interests.

Blue Cross Association president Walter McNerney says defensively, "We have the same frustration any social institution has finding a representative consumer. Once the person is a board member, he is no longer a private consumer. How to be democratic and not get bogged down is a very difficult logistical problem."

Consumer Control Held Key

Apparently, allowing subscribers to elect their own representatives gets "too bogged down" since it is limited to 8 plans, including the Philadelphia one. In most plans, they are selected by the incumbent board. In 21 plans, they are selected by the hospital representatives.

Consumer control, Dr. Denenberg believes, is the key to regulating the Blues. "That makes the whole thing of the Blues entirely different and puts the right focus on things," he says with satisfaction. While control may not be possible or even desirable, significant consumer input could help resolve some of the controversies involving the Blues.

Hazard to Navigation?

A lady of 70, Jana Weaver Thomas, riding the city streets of Freeport, Ill., in an afghan-draped motorized wheelchair, has the city fathers in a spin. A notary public and tax consultant, Mrs. Thomas has been making her rounds helping people with their taxes for free. The city council, however, claiming that she was disregarding traffic laws, recommended passage of an ordinance making her wheelchair illegal on city streets.

Continuous Fetal Monitoring Urged in All Labor Patients

Medical Tribune World Service

PRAGUE—Continuous monitoring of the fetal heart rate (FHR) combined with fetal blood analysis should be routine for all patients admitted to labor, and should not be limited to high-risk cases, according to a report submitted to the Fourth European Congress of Perinatal Medicine by Prof. R. W. Beard and Dr. P. T. Edington, of St. Mary's Hospital, London.

The procedure and the interpretation of results can be handled by a relatively inexperienced staff and should be made part of the midwife's responsibilities, the authors said.

In the section of London served by St. Mary's obstetric unit, the perinatal mortality was reduced from 29.3 per 1,000 birth in 1972, when only high-risk cases were monitored, to 15.6 in 1973, when 86 per cent of all women in labor were monitored.

Antepartum Mortality Unimproved

In 1973, intrapartum and first-week neonatal deaths numbered one and four, respectively, in 1,092 birth, compared with seven and 14 in 988 births the year before. Four of the seven intrapartum deaths in 1972 could have been avoided if the mothers had been monitored, in the authors' judgment, and early detection of intrapartum aspbyxia might have saved the 14 who died during the first week of life.

Antepartum mortality was not improved by monitoring, and the number of deaths rose from eight in 1972 to 12 in 1973. The death of the fetus during the last 12 weeks of pregnancy was described as "an unsolved problem despite the ready availability of urinary estrial and fetal cephalic biparietal measurement."

Of the 851 patients who were monitored in 1973, 739 (or 81 per cent) had a scalp electrode applied; the rest had the FHR recorded by external ultrasound or phonocardiography. Fetal blood samples were collected in 18 per cent (164 patients), which corresponded approximately to the incidence of suspicious FHR tracings. However, of these, 77 per cent proved to have a fetal pH within the normal range (more than 7.5).

An analysis of 806 FHR tracings showed that there was no significant correlation between the distribution of FHR patterns and complicated or uncomplicated pregnancies.

"This suggest that either high-risk factors or, alternatively, abnormalities on the continuous FHR, used on their own, are of little use for predicting that the fetus is asphyxiated," the investigators observed.

FHR Variability

► FHR variability appears to be an important indicator of fetal well-being, while FHR smoothness should be regarded as a suspicious finding and potential causes should be explored according to Dr. Richard H. Paul of University of Southern California Medical Center, Los Angeles.

Fetal pH levels were assessed 198 times, and FHR patterns and variability were observed for the 20 minutes immediately preceding these determinations. It was found that the mean pH values were consistently lower in the groups with minimal variability, and these differences were statistically significant.

To study the possible significance of variability in predicting newborn condition, the FHR variability was evaluated in 167 fetuses and newborns for 20 minutes immediately preceding birth. FHR variability was the sole factor judged; FHR pattern was not considered. The mean Apgar scores in newborns at both one and five minutes were higher in those who had demonstrated good FHR variability in utero, regardless of FHR patterns.

FHR smoothness is more difficult to evaluate, Dr. Paul said, since it is associated with a variety of conditions, and techniques for correlating lack of variation with particular circumstances are not yet available for clinical use.

Renal Graft Survival Boosted 12% With ALG

By BEN ROSE

Medical Tribune World Service

WINNEPEG, Man.—An increase of 11.72 percent in renal graft survival and a decrease of 37.5 percent in major graft rejection episodes has been achieved with the use of the immunosuppressive agent anti-lymphocyte globulin (ALG) the annual meeting of The Royal College of Physicians and Surgeons of Canada was told here.

Hailing the study as the first controlled clinical trial in the world with a standardized pool of ALG, Dr. H. E. Taylor director of the awards program Medical Research Council of Canada, Ottawa, said he expected future widespread use of ALG by surgeons to control episodes of transplant rejections.

The trial, carried out in nine Canadian cities, covers 87 patients given ALG and 92 patients randomly chosen as the control group. In the first three months, only 10 patients in the ALG group experienced a major rejection episode, compared to 30 in the controls. This improvement is statistically significant, Dr. Taylor said, and the 11.72 percent increase in graft survivals, although not statistically significant, is nearly so.

The survival rate of patients has been 90 percent in both groups, Dr. Taylor said, with ALG showing no impairment of patient survival. Also, he said, ALG did not appear to increase the infection rate. The ALG was given intravenously, 20 mg./Kg. body weight daily for 10 days post transplant.

Not a General Answer

Dr. Taylor said, however, that he does not expect ALG to be of value in heart transplants or as an answer to transplant problems generally.

Less prednisone was given to the ALG group in the 90 day post transplant period and there will be a follow-up to see if this leads to a reduction in corticosteroid complications. The creatinine studies show a better functioning kidney in the 90 days, Dr. Taylor said.

The most important complication was thrombocytopenia, frequently severe, but in spite of this, significant bleeding was not reported. Dr. Taylor said the thrombocytopenia was most likely due to a cytotoxic antiplatelet antibody.

Thymus gland obtained at open heart surgery was the antigen used to produce ALG. The first patient was taken into the study in October, 1971, and the intake ended last July with a total of 179.

There was some problem in infections when a central catheter was being used but this cleared up when a switch was made to a shunt site.

13 Kidney-Stone Groups

Medical Tribune World Service

BUDAPEST—A thermoanalytic process developed by the research staff of the urological clinic of the Semmelweis University Hospital here has made possible the identification of 13 major groups of kidney stones on the basis of their composition. The technique registers chemical changes in the stones caused by heat.

Educational Jukebox

A "medical education jukebox" has been installed at Albany Medical Center. Instead of music, medical and nursing students choose from 60 selections ranging from "Care of the Patient in the Immediate Postoperative Period" to "Recognition of Homicide."

ECTOPIC BEAT

A university release announces that "George W. Barnart of the University of Chicago has been awarded the Exalted Order of the Bumblebee."

—From the Queen Bee, no doubt. Bzzzzzzzzz

index

CLINICAL NEWS NOTE: "These results reveal [counterimmunoelectrophoresis] on spinal fluid to be of practical value as a clinical laboratory procedure for augmenting present methods of establishing bacterial etiology in patients with meningitis." (Drs. George M. Converse and J. Owen Hendley, see pg. 1.)

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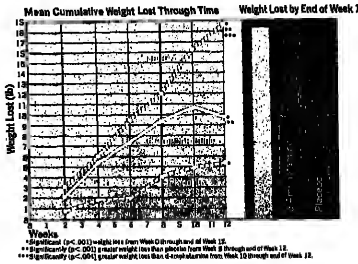
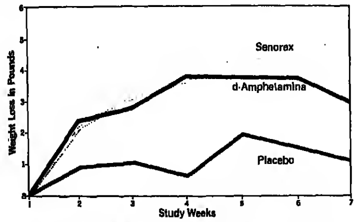
AS EFFECTIVE AS d-AMPHETAMINE



*Significant (p<.001) weight loss from Week 0 through end of Week 12.
**Significantly (p<.001) greater weight loss than placebo from Week 8 through end of Week 12.
***Significantly (p<.001) greater weight loss than d-amphetamine from Week 10 through end of Week 12.

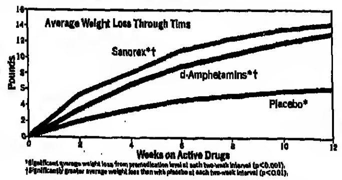
In a double-blind study[1] of 40 obese patients (all of whom completed the study), Sanorex (1 mg t.i.d.) was more effective than either placebo or d-amphetamine (5 mg t.i.d.) in helping patients lose weight.

The 14 patients on Sanorex experienced a substantially greater mean weight loss—1½ to 2 lb/wk, as compared with 1 to 1½ lb/wk for the 14 d-amphetamine patients—throughout the 12-week phase of active medication. After the sixth week, the superiority of Sanorex became increasingly evident. And as treatment progressed, so did weight loss in patients on Sanorex—whereas after the tenth week, patients on d-amphetamine began to regain some weight.



In a double-blind study[2] of 90 obese patients (59 of whom completed the study), Sanorex (1 mg t.i.d.) was more effective than either placebo or d-amphetamine (5 mg t.i.d.) in helping patients lose weight.

By the end of the third week of active medication, weight lose in the 20 d-amphetamine patients began to plateau, and by the end of the fifth week, these patients began to regain some weight. On the other hand, the 18 patients on Sanorex continued to lose weight throughout the six-week course of therapy.



*Significant average weight loss from premedication level at each two-week interval (p<0.001).
†Significantly greater average weight loss than with placebo at each two-week interval (p<0.01).

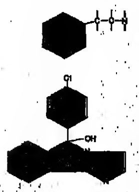
In a double-blind study[3] of 93 obese patients (all of whom completed the study), 30 patients received Sanorex (1 mg t.i.d.), 31 received placebo, and 32 received d-amphetamine (5 mg t.i.d.).

During the 12-week phase of active medication, patients on Sanorex lost an average of 14.1 lb, compared with 13.1 lb for d-amphetamine patients and 5.6 lb for placebo patients. Throughout the active medication phase, 63% of patients on Sanorex lost more than 1 lb/wk, compared with 38% of the d-amphetamine group and 29% of the placebo group.

BUT WITH CERTAIN DIFFERENCES

Although the pharmacologic activity of Sanorex and that of amphetamines are similar in many ways (including central nervous system stimulation in humans and animals, as well as production of stereotyped behavior in animals), animal experiments suggest that there are differences.* Sanorex also differs in basic chemical structure from amphetamines and all other prescription anorexiants.

Different Chemical Structure



An important chemical similarity between amphetamines and all other prescription anorexiants except Sanorex is the basic phenethylamine structure to which their differentiating chemical radicals are attached.

An important chemical difference between Sanorex and all other prescription anorexiants is that Sanorex is an isoindole; it does not contain a phenethylamine structure.

Different Neurochemical Action

Action of d-Amphetamine In animal studies, d-amphetamine (like intake of food) activates afferent neurons leading to appetite centers in the hypothalamus. Resulting release of norepinephrine activates the receptor neurons. Unlike food, however, d-amphetamine also suppresses norepinephrine synthesis. Thus, increasingly larger doses of d-amphetamine become necessary to produce an effect.*

Action of Sanorex (mazindol) After intake of food stimulates the release of norepinephrine from the afferent neuron, Sanorex blocks its re-uptake without disturbing normal synthesis and release.*

*The significance of these differences for humans is uncertain.

Simplicity and Flexibility of Dosage

Simple one-a-day dosage is facilitated by 2-mg tablets (taken 1 hour before lunch).

New flexibility (for the patient in whom 1 mg t.i.d. is preferred) is now facilitated by new 1-mg tablets (taken 1 hour before meals).

For Brief Summary, please see facing page

SANOREX® (MAZINDOL)©

References
1. Kornheber A: Problems and current concepts in the treatment of obesity. Scientific Exhibit presented at the New York State Academy of Family Physicians 25th Annual Scientific Convention, McAfee, NJ, May 8–10, 1973.
2. DeFelice EA, Chaykin LB, Cohen A: Double-blind clinical evaluation of mazindol, dextroamphetamine, and placebo in treatment of exogenous obesity. Curr Ther Res 15:358–366, July 1973.
3. Vernace BJ: Practical considerations for managing obese patients: Initial interview and effective treatment in the office. Scientific Exhibit presented at the American Medical Association, 27th Clinical Convention, Anaheim, Calif, Dec 1–4, 1973.

Indication: In exogenous obesity, as a short-term (a few weeks) adjunct in a weight reduction regimen based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors.
Contraindications: Glaucoma; hypersensitivity or idiosyncrasy to the drug; agitated states; history of drug abuse; during, or within 14 days following, administration of monoamine oxidase inhibitors (hypertensive crisis may result).
Warnings: Tolerance to many anorectic drugs may develop within a few weeks; if this occurs, do not exceed recommended dose, but discontinue drug. May impair ability to engage in potentially hazardous activities, such as operating machinery or driving a motor vehicle, and patient should be cautioned accordingly.
Drug Interactions: May decrease the hypotensive effect of guanethidine; patients should be monitored accordingly. May markedly potentiate pressor effect of exogenous catecholamines; if a patient recently taking mazindol must be given pressor amine agents (e.g., levarterenol or isoproterenol) for shock (e.g., from a myocardial infarction), extreme care should be taken in monitoring blood pressure at frequent intervals and initiating pressor therapy with a low initial dose and careful titration.
Drug Dependence: Mazindol shares important pharmacologic properties with amphetamines and related stimulant drugs that have been extensively abused and can produce tolerance and severe psychologic dependence. Manifestations of chronic overdosage or withdrawal with mazindol have not been determined in humans. Abstinence effects have been observed in dogs after abrupt cessation for prolonged periods. There was some self-administration of the drug in monkeys. EEG studies and "liking" scores in human subjects yielded equivocal results. While the abuse potential of mazindol has not been further defined, possibility of dependence should be kept in mind when evaluating the desirability of including the drug in a weight-reduction program.
Usage in Pregnancy: In rats and rabbits an increase in neonatal mortality and a possible increased incidence of rib anomalies in rats were observed at relatively high doses. Although these studies have not indicated important adverse effects, the use of mazindol in pregnancy or in women who may become pregnant requires that potential benefit be weighed against possible hazard to mother and infant.
Usage in Children: Not recommended for use in children under 12 years of age.
Precautions: Insulin requirements in diabetes mellitus may be altered. Smallest amount of mazindol feasible should be prescribed or dispensed at one time to minimize possibility of overdosage. Use cautiously in hypertension, with monitoring of blood pressure; not recommended in severe hypertension or in symptomatic cardiovascular disease including arrhythmias.
Adverse Reactions: Most commonly, dry mouth, tachycardia, constipation, nervousness, and insomnia. *Cardiovascular:* Palpitation, tachycardia. *Central Nervous System:* Overstimulation, restlessness, dizziness, insomnia, dysphoria, tremor, headache, depression, drowsiness, weakness. *Gastrointestinal:* Dryness of mouth, unpleasant taste, diarrhea, constipation, nausea, other gastrointestinal disturbances. *Skin:* Rash, excessive sweating, clamminess. *Endocrine:* Impotence, changes in libido have rarely been observed. *Eye:* Long-term treatment with high doses in dogs resulted in some corneal opacities, reversible on cessation of medication; no such effect has been observed in humans.
Dosage and Administration: 1 mg three times daily, one hour before meals, or 2 mg per day, taken one hour before lunch in a single dose.
How Supplied: Tablets, 1 mg and 2 mg, in packages of 100.
Before prescribing or administering, see package circular for Prescribing Information.

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Plastic Surgery Mitigates Xeroderma Pigmentosum

Medical Tribune World Service

BRNO, CZECHOSLOVAKIA—Xeroderma pigmentosum (Kaposi's disease), a rare inherited skin disease usually beginning in childhood and characterized by disseminated pigment spots, telangiectasis, and atrophy in exposed areas of the skin, leading to malignancies and frequently ending in death, has been considerably mitigated by plastic surgery in a young boy according to Prof. Vojtech Kubácek, director of the Department of Plastic Surgery, Purkyne Medical School here.

The patient was first seen in 1963 as a seven-year old boy with a fully developed case of the disease, including spinocellular carcinomas on the left lower eyelid, left cheek and upper lip, but whose general condition was not yet seriously affected.

Signs of the disease on affected skin transplanted to the abdomen have almost disappeared.

Diseased skin from the dorsum of the right hand implanted into the left side of the hypogastrium developed a thick horny scale, above, under which the skin is without disease, right.

Prof. Kubácek replaced the entire skin of the face, the back of the neck, and the back of both hands with skin from sites on the abdomen and thorax which, not having been exposed to light, did not show any signs of the disease.

During the period of treatment, which lasted for several years, the tumor on the upper lip and columella of the nose recurred three times and had to be treated by radical surgery and reconstruction, using skin flaps from the hypogastrium.

No Disease for 3 Years

The transplanted skin showed no signs of the disease during the following three years, after which minute pigment spots began to appear without hyperkeratosis, and these have persisted up to the present, eleven years after the patient was first seen, but no signs of malignancy have ever appeared on the transplanted skin, and the patient's general condition has improved.

To verify that transplantation itself reduces the intensity of the disease, Prof. Kubácek transplanted affected skin to the patient's abdomen where it was protected from light, and to his forearm where it was still exposed to external influences. Both these transplants took well and lost the characteristic signs of the disease.

Diseased skin from the back of the right hand which was implanted on the left side of the hypogastrium developed a thick horny scale under which the skin has shown no signs of the disease up to the present day.

Prof. Kubácek has not yet found an explanation for the fact that while the transplantation does not affect the root cause of xeroderma pigmentosum it obviously does render the skin less vulnerable to the disease, since certain typical changes take place in the transplanted skin.

Affected skin transplanted to forearm has lost its typical disease character.

Menstrual Regulation Effective for Fertility Control in Singapore

Medical Tribune World Service

BUENOS AIRES—Menstrual regulation has been found highly effective for fertility control among Singapore women, the Eighth World Congress of Fertility and Sterility was told here.

Dr. D. Vengadasalam, Kandang Kerbau Hospital, Singapore, reported that 600 women whose periods were overdue 14 days or less underwent menstrual regulation at the hospital after requesting medical treatment.

The method used was suction curettage with a 50-cc. Karman's plastic syringe fitted with a 4-, 5-, or 6-mm. plastic cannula to start menstrual bleeding. It was done as an outpatient procedure without anesthesia or analgesia.

None of the women had a positive pregnancy test and/or signs or symptoms of pregnancy at follow-up examination.

Only two complications (0.33 per cent) were encountered, Dr. Vengadasalam reported. There were no technical difficulties, he said, and no additional operative procedures were required.

Contraceptive acceptance was high among women who were offered contraceptive counseling after menstrual regulation. Dr. Vengadasalam termed menstrual regulation a useful addition to fertility control methods.

Co-workers in the study were Dr. T.H. Lean, of Kandang Kerbau Hospital, and D.A. Edelman, Ph.D., International Fertility Research Program, University of North Carolina.

Lung Cancer Deaths Drop After Tar Cut in Australia

Medical Tribune World Service

MELBOURNE—About 100 fewer Australians between 55 and 65 died last year of lung cancer, according to the Anti-Cancer Council of Victoria. The decrease followed a sharp reduction in the tar content of Australian-made cigarettes over the past five years.

The decline in deaths in the 55-65-year-old group came at a time when the annual mortality from lung cancer was still rising.

The director of the council, Dr. Nigel Gray, said that an antismoking drive, along with the lowering of cigarette tar content was having an effect.

No Ethnic Bias Discerned In US-Funded Sterilizations

Medical Tribune Report

WASHINGTON—A study of sterilizations performed on women in 101 federally funded family planning projects has shown that age and parity—not ethnic group—are main factors determining whether patients elect this method of birth control.

Another finding of the study, which was made by Denton Vaughan and Gerald Sparer of the Department of Health, Education, and Welfare, is that sterilization rates "are not very different" for welfare recipients compared to nonrecipients if age and parity are taken into account.

The data covered all projects except those in Puerto Rico reporting at least 20 sterilization patients of either sex during 1972. Of about 550,000 women who attended the clinics, 5,969 received sterilization as a medical service.

Actual sterilization rates per 1,000 family planning patients were higher among women of Latin American descent (16.8) and black women (12.6) than among Anglo women (8.3), according to the study reported in *Family Planning Perspectives*.

But patients in the first two of these ethnic groups tended to be older than the Anglo women and to have had more children at the time a sterilization decision was made. Within each specific age and parity group, Anglo women "generally were more likely to be sterilized" than black women or those of Latin American descent.

The relationship between parity and sterilization was particularly clear, the investigators noted. The combined rates for women of all three ethnic groups ranged from a low of 1.5 sterilizations per 1,000 patients at zero parity to over 50 per 1,000 at a parity of five or more.

The highest single rate—115.6 per 1,000—was found among women aged 20 to 24 with five or more children.

Welfare status proved to be a relatively minor factor in sterilization rates when figures were controlled for age and parity.

Although the actual rates were more than twice as high for recipients as for nonrecipients of welfare, four-fifths of this difference disappeared when the women were considered by age and family size at time of sterilization.

Nonwhite recipients of public assistance, however, had about one-third more sterilizations than did nonwhite nonrecipients even when age and parity were controlled.

Differences between recipients and nonrecipients may, the report says, turn out to be artifacts of the study procedure and in any case are "too small for it to be likely that there is any overall bias directed against nonwhite welfare recipients through Federally supported projects."

But the investigators emphasize that their data "can shed no light on whether or not Federal Medicaid or Title IV-A funds are being used to reimburse physicians who may attempt to coerce welfare patients to accept sterilization."

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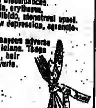
(diethylpropion
hydrochloride N.F.)

BRIEF SUMMARY
INDICATION: Tenuate is indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.
CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma.
Agitated states.
Patients with a history of drug abuse.
During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).
WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.
Drug Dependence: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There are occasional reports of subjects dependent on amphetamine later chronically abusing diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia.
Use in Pregnancy: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks.
Use in Children: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension.
Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen.
Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride.
Central Nervous System: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported.
Gastrointestinal: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances.
Allergic: Urticaria, rash, ecchymosis, erythema.
Endocrine: Impotence, changes in libido, menstrual upset.
Hematopoietic System: Bone marrow depression, agranulocytosis, leukopenia.
Miscellaneous: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, and polyuria.



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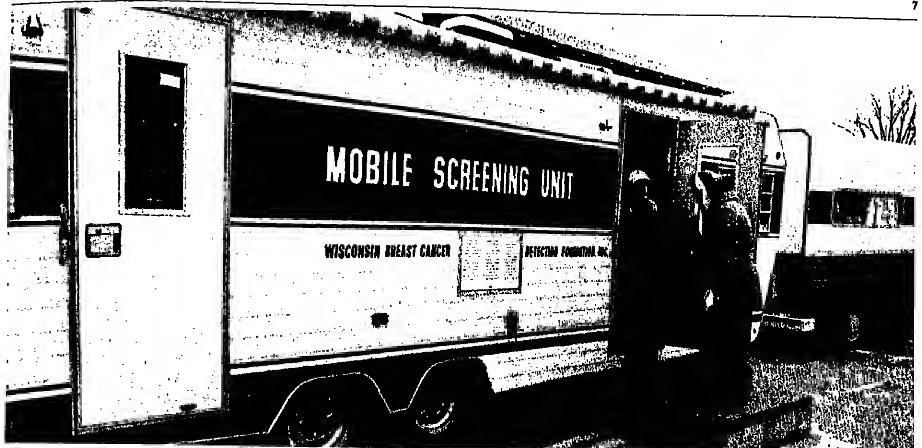

Using mobile trailers and taking them to locations like shopping centers, the Wisconsin program has been able to screen as many as 1,100 women in 53 hours.

Wis. Breast Screenings Highlight Benefits of Mobile Thermography

THE WISCONSIN Breast Cancer Detection Foundation has screened more than 20,000 women for breast cancer, using thermography, in mobile units. Since personnel and equipment are inadequate for mammography in every woman, a different method must be used for mass screenings. The advantage of thermography is that large numbers can be screened in a short time to select the high-risk population for subsequent x-ray and clinical studies. The Wisconsin group has found that the mobile thermography program brings good screening immediately to all areas at the least expense and helps expand mammography facilities and education. Interpretations of the thermograms were sent to personal physicians, along with a copy of the actual thermogram, to familiarize the professional population with this screening procedure.

About 15 per cent of the persons tested at each session will be referred for clinical examination and mammography study due to a suspicious thermogram.

The mobile units also provide instruction in self-examination.

Family histories are taken at the screenings, and any woman with a family history of breast cancer is recommended for a mammogram, no matter what the report of the thermogram reading is.

If there's good reason to prescribe for psychic tension...

When, for example, reassurance and counseling on repeated visits are not enough.

Effectiveness is a good reason to consider Valium® (diazepam)

After you've decided that the tense, anxious patient can benefit from antianxiety medication, the question remains: which one?

Valium is one to consider closely. One that can help to relieve the psychic tension and anxiety. One that can minimize the patient's overreaction to stress. One that is useful when somatic complaints accompany tension and anxiety. In short, one that can work and work well to help bring the patient's symptoms under control.

Effectiveness. One good reason to consider Valium.

And should you choose to prescribe Valium, you should also keep this information in mind. Valium is generally well tolerated in the recommended dosage ranges. However, the physician should be aware of the possibility of side effects in some patients and should consult complete product information before prescribing.

Please turn page for a summary of product information.

Valium®
(diazepam)
2-mg, 5-mg, 10-mg tablets

ROCHE

Valium® (diazepam)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 100.

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The Crisis at the Pasteur Institute

Continued from page 1

ter? If this be the fate of an institution which is justifiably a national glory of a major scientific state whose subsidies —however inadequate—support it in part, can private, unsubsidized, commercial organizations fare better? Few if any individual national institutions or private organizations can match the traditions or basic research competence of the Pasteur Institute. Consider also that the intrinsic brilliance and social dedication of the Pasteur'n scientists can also be brought to bear on such less demanding functions as manufacture and distribution. If the Pasteur Institute's survival without adequate "profits", without patents and trademark protection is at risk, then its future contributions to the good of man are in jeopardy. *It is incredible but true that the very circumstances which threaten the continuity of the Pasteur Institute are being advocated as the "proper" way to manage the future of our entire medicinal research and production establishment.*

If the Pasteur can't make it under its self-imposed strictures of the past, can private institutions long prosper and survive under governmentally imposed similar strictures? Is this a goal to be desired?

We are reaching the point of no return. The lavish investments in research of private pharmaceutical organizations cannot be long sustained under present circumstances, even less so under the no-patent, no-royalty strictures which have been fiscally strangling a semi-subsidized, quasi-public institution such as the Pasteur Institute. To a cool-headed and clear-eyed accountant with a sharp pencil, present pharmaceutical research costs cannot long be justified by future potential profits. When administrators in industry awaken to this reality, an awakening that is inevitable, there will be a reduction of research expenditure to accord with the risks and rewards. To increase risks constantly and simultaneously diminish rewards is a formula for destruction of the viability not only of quasi-public but of private medical research and service organizations as well. This formula is illogical and senseless.

Let us remember that those who have the most to lose from the constriction of research are those who are the least affluent, those who are the most frequent victims of illness and premature death. We—our families and friends, and, above all, our individual patients—must also ultimately pay the price of governmental regulations that impose a *status quo* in medical research and medicinal therapy. A.M.S.

More Than a Ray of Hope

FROM ITS earliest days, MEDICAL TRIBUNE has been interested in automotive safety and has emphasized the triad of the car, the driver and the roadway—and the need to effect improvements in each. Until 1971, we featured an annual editorial that analyzed the preceding year's record of motor vehicle fatalities. The last such editorial was in 1971 when a ray of hope was discerned. Until 1969, there had been a large yearly increment in traffic deaths, rising, for example, from about 43,000 in 1963 to over 56,000 in 1969. In 1970, some 55,300 people died in traffic accidents, a decline of 1,100 from the figures for 1969.

We have been keeping our fingers crossed since that editorial and observing statistics with increasing hope, for between 1969 and 1973 automobile fatalities had more or less plateaued and the steep annual rise of the recent past was no longer evident. Death rates per 100,000,000 vehicle miles from 1968 on exhibited an increasingly favorable trend and it seemed likely that campaigns for automotive safety were finally bearing fruit.

Last year has been the most extraordinary of all in improvement of the record for traffic deaths. The estimate is that there were about 45,400 automobile fatalities in 1974; such deaths totaled 55,100 in 1973. This precipitous drop in traffic deaths is also reflected in the death rate per 100,000,000 vehicle miles. It has fallen from 4.2 in 1973 to 3.5 in 1974.

This dramatic improvement has been attributed by most safety experts to the national 55-mile an hour speed limit introduced last year in partial response to the energy crisis. Amitai Etzioni, the Columbia University sociologist, in an editorial in *Science* seized upon this as an example of how a social problem is "drastically affected by factors neither foreseen nor deliberately introduced for the purpose." He is, of course, correct in noting that this speed limit was introduced to save gasoline and not lives. But what it has done is to accelerate a trend that was already evident beforehand—and not to bring it about *de novo*.

Confronting Pain

CLINICAL QUOTE: "... *Face-to-face group discussion is much more effective and productive in making a correct diagnosis and formulating the appropriate therapeutic strategy than communication by letter or telephone or through fragmented independent efforts inherent in traditional medical practice.*" *(Dr. John Bonica, reporting on a multidisciplinary pain clinic for referred patients, A.A.A.S. meeting,* *see page 13).*

"It's beating quadraphonically!"

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LETTERS TO TRIBUNE

Government Prescribing

My sincere thanks for your recent articles in Medical Tribune, particularly the editorial "Mischievious Meddling" and Dr. Seckler's column on "The Price of Drugs, Patient Privacy and the Physician-Patient Relationship" (MT, Jan. 29).

Because of the lack of information available to (or used by) the public press we have been having a rough time getting the word to the people. We talk to patients when time permits. Otherwise, we have to fall back on "Letters to the Editor"—particularly in those papers whose editorial policy is controlled outside the community. I enclose a couple of samples.

Despite the general ignorance, protests have come from: 1. Texas Medical Ass'n; 2. All Saints Hospital Staff; 3. Tarrant County Academy of Family Practice; 4. Board of Directors, Tarrant County Medical Society.

Most local druggists are opposed to MAC (Maximum Allowable Cost) proposals, but one has spoken up.

The stated A.M.A. policy against compulsory generic prescribing originated some years ago in this local medical society. I'm positive about this as I wrote the original resolution which went up the line unchanged.

MAL RUMPH, M.D.
Fort Worth, Texas

Preventive Health Insurance?

I fully agree with Ralph Nader's views that we are—and have been—neglecting prevention (MT, Feb 5). It's important to bear in mind that the insurance companies are aiding and abetting this narrow view of the function of medicine. For example, Greater N.Y. Blue Shield pays *no* benefits for *any* preventive medicine: annual physicals, immunization, or any lab work which is part of a routine check-up and not needed to treat "disease."

Government agencies share this responsibility. Thus, the V.A. demands "service connection" before it will treat veterans, and does not recognize delayed onset of post-combat syndromes. The armed forces processed millions of men back into civilian life at a speed (15 min./man) which made the detection of incipient disorders impossible. Nader's Veterans' Task Force itself analyzed some of these shortcomings very cogently ("Vietnam Veterans—The Discarded Army," by Paul Starr).

Unfortunately, these monolithic third parties—none of them representing the consumers—now play the decisive role in deciding how much preventive medicine will be made available to the population at large.

CHAIM F. SHATAN, M.D., C.M.
Professor, Psychoanalytic Training Program
New York University, New York

"Shotwise"

In re: Dr. Charles B. Moore's "This is Medical Ethics?" (MT, Jan. 22). Amar and I agree with the Padre, bless him. May I add an addendum to his seventh problem: — vitamins — especially "shotwise?" When I was a boy in the profession it was an iron-arsenic preparation.

DAVID MARTH, M.D.
Class 1920
Santa Cruz, Calif.

Correction

One apologies to Dr. Sheldon G. Gilgore, president of Pfizer Pharmaceuticals and vice-president of Pfizer Inc., for misspelling his name, February 19.

Aorta-Coronary Vein Bypass Effective in Selected Cases

Continued from page 1

patients with intractable angina pectoris and previous revascularization failure who underwent aorta-to-coronary-vein saphenous vein bypass grafting. Drs. Thomas L. Buhl and R. Peter Henney were coauthors.

All patients survived and were either partially or completely relieved of their symptoms. Of the four grafts performed—one double and two single bypass procedures—two out of three tested postoperatively by cineangiograms were patent, and the graft in the untested patient is presumed patent because of his absence of symptoms and his performance on a stress ECG.

Experimental Work

In the initial experimental work in dogs, the investigators ligated the anterior descending coronary artery and then constructed free femoral vein bypass grafts from the ascending aorta to the anterior descending coronary vein. (The internal mammary artery was abandoned as unsatisfactory for these grafts after mean flow rates were all measured as less than 20 cc. a minute in initial trials.) The proximal coronary vein was also ligated to minimize shunting into the coronary sinus.

Mean flow rates through the aorta-coronary-vein grafts in the 18 dogs tested were less than 50 cc. a minute in three dogs, between 50 and 100 cc. in seven, and over 100 cc. in eight.

Further tests performed to determine postoperative patency and effectiveness of the grafts included coronary venous angiograms and measurement of the uptake of dye and radioactively labeled materials via the graft into the area where the arterial supply had been interrupted.

These tests, the fact that the coronary veins usually turned from blue to pink, and the fact that the cyanotic myocardium also regained its normal color in many instances, all suggested that significant revascularization was occurring.

The investigators regarded the experimental results as justifying clinical trials, and three patients with severe, persistent angina and previous revascularization failure were operated on last July and August.

3 Cases Described

Dr. Benedict gave this summary:

Case one: A 54-year-old man suffered intractable angina for which he had previously undergone percutaneous cordotomy. He was now addicted to oral dihydromorphinone. Multiple arteriograms had shown occlusion of the dominant right coronary artery and diffuse disease of both the anterior descending and circumflex arteries. Previous double Vineberg implants (1967) and a saphenous vein bypass graft (1972) were now all occluded, and ischemic electrocardiographic changes were visible upon atrial pacing.

The authors performed saphenous vein bypass grafting to the anterior descending coronary artery and to the posterior descending cardiac vein in July, 1974. Mean flow rates of 55 cc. per minute in the artery and 60 cc. per minute in the cardiac vein were measured at operation.

The patient left the hospital on the eighth postoperative day, free from pain and anginal use. Although he has remained so, a repeat angiogram two weeks later showed patency of the aorta-to-coronary-artery graft but occlusion of the aorta-to-coronary-vein graft.

Case two: A 45-year-old man suffered intractable angina for which he took 150 to 600 nitroglycerin tablets per month. Previous coronary angiograms demonstrated occlusion of both the right and the anterior descending coronary arteries, as well as severe stenosis of the diagonal and circumflex arteries. Only one of two Vineberg implants (1965) and one of three saphenous vein bypass grafts (April, 1974) remained patent.

In August, 1974, the authors constructed saphenous vein bypass grafts from the ascending aorta to the anterior descending cardiac vein (mean flow at surgery: 90 cc. per minute) and to the posterior descending cardiac vein (mean flow: 120 cc. per minute).

The patient had complete relief of his angina, and angiograms on the eighth postoperative day showed excellent visualization and patency of both grafts. Scanning studies also showed uptake of radioactive technetium and iodine by the myocardium via the graft.

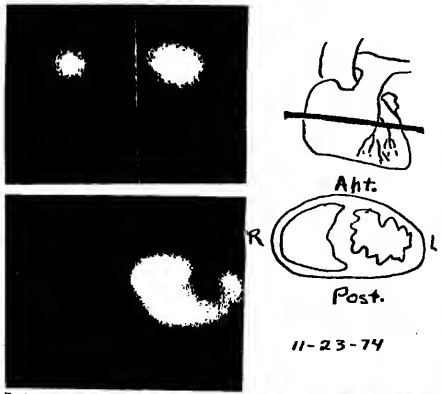
Asymptomatic on 8th Day

Case three: A 67-year-old man was transferred to St. Mary Medical Center with pain diagnosed as preinfarction angina. He had had previous infarcts in 1953 and 1967. Angiograms demonstrated occlusion of a large dominant circumflex trunk and severe stenosis of the anterior descending coronary artery. Although in heart failure prior to transfer, he was adequately compensated at the time of this admission.

In August, 1974, the authors constructed saphenous vein bypass grafts to the anterior descending coronary artery and to the circumflex vein. A pink flush appeared over the posterolateral region of the heart when flow through the vein, measured at 190 cc. per minute versus 50 cc. for the artery, was established.

The patient was asymptomatic at discharge on the eighth postoperative day. His treadmill stress ECG was normal, and he reported that he felt so well that he would not submit to repeat angiography. His grafts are presumed to be patent.

Dr. Benedict and his co-workers stressed that it is too early to tell what the long-term results of the procedure will prove to be regarding patency, the development of intramyocardial shunts, or hyperplasia of the coronary venous system. But they expressed the belief that the early clinical improvement in these three patients, coupled with evidence of retrograde capillary perfusion via grafts to coronary veins in experimental animals, indicates that further clinical trials are warranted.



Postmortem cross sections through myocardium of dog that underwent free femoral vein bypass graft from ascending aorta to anterior descending coronary vein. Upper photo shows two scans of I^{131} deposition following injection into graft going into coronary vein. Lower photo is of two scans of Te^{99} deposition after injection into coronary arteries, with "bite out" visible at right (dark finger extending into bright area) resulting from experimental occlusion of anterior descending coronary artery. Drawing at right shows level of sections.

The present indications, in their view, for considering aorto-coronary vein bypass grafts are:

- Patients with severe, intractable, incapacitating angina pectoris.
- Patients in whom previous bypass surgery to the coronary arteries has failed.
- Patients with large areas of ischemic muscle supplied by an artery that is found at surgery to be too small to accept a graft.
- Patients who require replacement of endarterectomy, especially in the left coronary system.
- Patients with diffuse disease, especially those who have maintained a well-contracting myocardium.

Indications for Carotid Angiography Cited by Cleveland Clinic Surgeon

Medical Tribune Report

CLEVELAND—Patients with carotid bruits that are loud or extend into diastole usually have significant carotid stenosis and should probably be considered for carotid angiography and possibly be subjected to carotid endarterectomy, Dr. Edwin G. Beven, of the department of vascular surgery at the Cleveland Clinic, said here.

So should patients with even less gross lesions who are about to undergo operative procedures involving the heart or aorta who might be in danger of cerebral vascular accident because of hypotension occurring either during the operative procedure, or immediately thereafter.

As a general rule, Dr. Beven told a symposium at the Clinic on "Controversies in Surgery," a patient with stenosis of 80 per cent or more should be operated upon.

"The patient with mild stenosis we do not operate, because we will have enough time to do so if it progresses, and if he develops transient ischemic attacks in the future. It is also advisable to have these patients followed by an ophthalmologist with carotid compression tonography, because this is a noninvasive, no-risk method."

Dr. Beven said that patients with lesser lesions should be seen about every six to 12 months, since "about 60 per cent of these lesions within four to five years are progressive, some slowly and some at a more rapid rate."

He recommended that the examination for such patients include determination of the subclavian and superficial temporal pulses, determination of blood pressure in both arms, and auscultation of the neck.

About 10 per cent of patients, he added, can be reassured that the problem is with the external carotid artery, and that the internal carotid is perfectly normal.

Fast Way to Determine Etiology of Meningitis

Continued from page 1

lumbar puncture were studied in order to determine the value of CIEP in partially-treated meningitis. Thirteen had positive CSF culture, 10 caused by Haemophilus influenzae, two by meningococcus and one by pneumococcus. Eleven had negative cultures.

Dr. Converse said CIEP was positive for bacterial antigen in 88 per cent of patients with H. influenzae meningitis, 37 per cent with meningococcal meningitis and 40 per cent with pneumococcal meningitis. The overall positive rate was 72 per cent.

In every case the antigen detected matched the cultured organism. There were no false positives or cross reactions. Specificity was established since CIEP was negative in the 11 non-bacterial meningitis patients, 6 neonatal patients and the 45 controls.

How Multidisciplinary Pain Clinic Functions

By MICHAEL HERRING
Medical Tribune Staff

NEW YORK—"Face-to-face group discussion [by consultants] is much more effective and productive in making a correct diagnosis and formulating the appropriate therapeutic strategy [for complex chronic pain] than communication by letter or telephone or through fragmented independent efforts inherent in traditional medical practice," Dr. John J. Bonica told listeners at the symposium on pain control at the 141st annual meeting of the American Association for the Advancement of Science here.

Summarizing the evolution, organization, and function of one of the country's first multidisciplinary pain clinics, Dr. Bonica began his address with a caveat against "viewing [chronic] pain in a very narrow, tubular fashion," which is a result of increasing specialization. He stressed conceptual changes in diagnosis, therapy, and research in pain that have occurred as a result of work at clinics such as the one he and Dr. Lowell White founded at the University of Washington in 1961.

DR. BONICA

Dr. Bonica, who is Professor and Chairman of the Department of Anesthesiology and Director, Anesthesia Research Center and Pain Clinic, University of Washington School of Medicine, said that the clinic there is currently composed of 20 individuals representing anesthesiology, general practice, physiatry, neurosurgery, nursing, oral surgery, orthopedics, pharmacology, psychintry, psychology, radiology, sociology, and surgery.

Clinic's Procedure

Patients with chronic pain are referred by their physician to the clinic, he explained, where a manager is appointed to serve as the patient's liaison with the rest of the team of specialists. After screening and a careful review of the history and other records from the patient's doctor, the patient's assigned clinic physician conducts a thorough examination, and determines which other members of the clinic the patient should consult.

Pooling results from the other consultants, the physician then attempts to diagnose the pain, Dr. Bonica said. If the diagnosis and therapy are clear-cut, he added, the patient is sent back to his referring physician or treated at the clinic.

For those whose diagnosis is still unclear, a conference is held in which the entire case is reviewed, open discussion ensues among all consultants involved, and the patient and his or her spouse are invited to ask and answer questions, Dr. Bonica stated.

This kind of conference, he said, is the unique contribution to diagnosis and therapy of pain that the multidisciplinary pain clinic is able to provide the medical community and the patient. In addition, he said, such clinics have altered the course of basic medical research.

Collaborative Research

In the beginning, "members of the group carried out independent research in their own laboratories. However, with the participation of psychologists, pharmacologists, and other basic scientists and clinical investigators there began interaction, cross-fertilization, and communication which has resulted in collaborative research.

"This has been one of the most gratifying 'spin-offs' of the group's activities," he concluded.

Bioavailability Tests In Vivo Held Essential For All Generic Drugs

Medical Tribune World Service

TORONTO—In vivo studies to determine bioavailability of every generic drug will continue to be necessary until much more clinical pharmacology of these drugs is known, Dr. William G. Barr, Professor and chairman of the Department of Pharmacy and Pharmaceuticals, Virginia Commonwealth University, said here.

Where plasma concentrations are critical, in vitro studies alone will not be sufficient to predict whether these drugs will reach their desired plasma levels, Dr. Barr told an international conference on "Prescription Drugs and the Patient's Health."

"Once we know the relationship between the plasma level and the therapeutic effect and the adverse effect, it will no longer be necessary to do a clinical trial of every generic drug," he said.

But to overcome this problem it is necessary to know what range of differences in plasma concentrations are acceptable and what differences may be clinically significant or hazardous, if they occur, he said.

The need of more information about the rate of absorption of drugs is a critical matter, Dr. Barr went on. If the rate of absorption is slow, there is a danger that patients will take more than one dose and suffer a cumulative reaction. "In the case of barbiturates," he said, "automatism (forgetting the number of doses) may account for a large number of deaths termed suicides. These deaths, in fact, may be related to bioavailability."

Now, for both aspects of constipation

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and hard dry stools

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Provides a unique natural laxative—standardized senna concentrate... virtually colon-specific ...effectiveness documented in numerous published studies comprising thousands of patients.

Provides a classic stool softener—DSS...complementing the laxative action by softening the stool for smoother and easier passage.

Comfortable, predictable evacuation... a bedtime dose of SENOKOT S Tablets usually induces comfortable evacuation the next morning, allowing uninterrupted sleep. SENOKOT S Tablets aid in rehabilitation of the constipated patient by facilitating regular elimination.

Indications: SENOKOT S Tablets offer welcome relief in functional constipation when combined neuroperistaltic stimulation plus stool softening is indicated, especially for: the aged; postpartum and postoperative patients; drug-induced constipation; cardiovascular patients and those with hemorrhoids. **Dosage** (preferably at bedtime): **Adults:** Initial Dosage: 2 tablets (max. dose—4 tablets b.i.d.). **Children** (above 60 lb.): 1 tablet (max. dose—2 tablets b.i.d.). To meet individual requirements, dosage may be decreased or increased by 1 tablet (up to maximum) until the most effective dose is established. **Supplied:** Bottles of 30 and 60 tablets.

PURDUE FREDERICK

8 Nobel Laureates Among Pasteur's Successors

Medical Tribune World Service

PARIS—Louis Pasteur was both scientist and communicator. And it was his skill in public relations, allied to his genius as a researcher, that brought the Pasteur's Institute into being in 1888.

By then Pasteur was 66, and suffering from hemiplegia.

The building was financed by a national subscription, the success of which was largely due to the public enthusiasm created by Pasteur's discovery of a rabies vaccine.

Pasteur's other achievements were legion: work in crystallography which was to lay the foundation of the new science of stereochemistry; the demonstration of the mechanism of fermentation; research on the diseases of silkworms; identification of a series of previously unknown pathogens, including staphylococcus, streptococcus and pneumococcus; and the prevention of infection in surgery by aseptic techniques.

It was with Jenner in mind that Pasteur agreed to try to save the life of a boy called Joseph Meister, bitten 14 times by a rabid dog. Pasteur had already put the vaccine to the test with animals. Could a human patient develop immunity to the virus in the period before multiplication began in the body? He believed it was possible, and injected the boy with attenuated vaccine on July 6, 1885. The boy was saved, and a tradition was established.

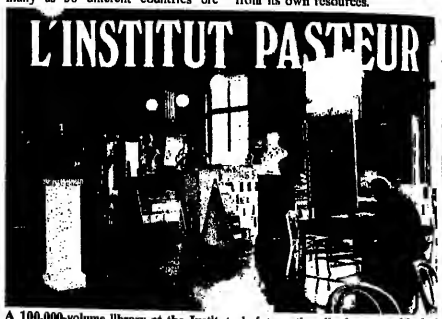
8 Nobel Prizes to Staff

Carrying on the work of Pasteur, who died in 1895, the Institute's staff have since then been awarded eight Nobel Prizes. The savants so honored were Charles Laveran (1907) who discovered the malaria-bearing protozoa, Elie Metchnikoff (1908), one of the founders of the science of immunology, Jules Bordet (1919) for work showing the role of antibodies and complement, Charles Nicolle (1928), who first realized that the louse can transmit typhus, Daniel Bovet (1957) antihistamines, and the 1963 trio, François Jacob, André Lwoff, and Jacques Monod—the genetic regulation of enzyme synthesis.

Today, more than 1,000 persons work at the Institute, which has become a center for teaching and research in bacteriology and virology, cellular and molecular biology, microbiology, and immunology. The research is linked, on the one hand, with a 100-bed hospital specializing in infectious, parasitic, and immune diseases, and on the other, with a production center for the mass manufacture of vaccines, serums and reagents.

The Institute also has an international vocation. In an average year as many as 50 different countries are represented among its postgraduate students, including many from the United States. At the same time the laboratories act as an international reference center for the World Health Organization, identifying and providing microbial strains, and acting as a national, regional and international focus for epidemiological surveillance.

The Institute, which has 16 branches overseas, is financed 70-80 per cent from its own resources.



A 100,000-volume library at the Institute is internationally famous, with about 30,000 persons using it each year. The Institute was founded after Pasteur's results with the rabies vaccine were so striking as to bring a national subscription.

Historic instruments, above, used by Pasteur and co-workers for the extraction of attenuated rabies virus from rabbit brains. Left, a fully masked worker examines germ free animals. As many as 50 different countries will be represented among the postgraduate students each year at the Institute.

A model for an influenza virus developed by Pasteur investigators. The laboratories act both as a national center and an international lab for WHO, particularly for bacteria, the rabies virus, the arboviruses, and influenza viruses.

A display of Pasteur's laboratory equipment also shows a picture of his early work in inoculating sheep.

One Man...and Medicine

ARTHUR M. SACKLER, M.D.,
International Publisher, Medical Tribune

Vicissitudes of the Pasteur Institute-Part II

THE PASTEUR INSTITUTE has since its founding wedded basic science to Pasteur's mission "to deliver man from the calamities which beset him." Pasteur's mind was so penetrating that his solutions to agricultural and industrial problems laid the fundamental principles of new sciences. In keeping with the Pasteur injunctions, the Pasteur Institute has since then sought to convert pure science at "its highest level" to "bring profit to man from the application of its precious results." As Pasteur put it, "There is only science and the application of science related to each other as the fruit is related to the tree which bore it."

For over eighty years the Institute has made its discoveries and know-how available without license. Now, belatedly but we hope not too late, there is recognition that its production of low cost vaccines without patent or trademark protection has undermined the fiscal viability of the Pasteur, jeopardizing its very existence. One can imagine the distaste with which Monod confronted the dilemma of making products inexpensively available without patent and the unpleasant reality that

"If the Institute had earned royalties on the vaccines it produced, there wouldn't be any financial problem."

Monod's Attitude

These are not the words of a profit hungry, money-grubbing capitalist. Jacques Monod has been described philosophically as an individualist with his own passionate brand of socialism—an "anti-state, decentralized socialism." He has a distaste for bureaucracy which, he is convinced, "would stifle the creative excellence of the Pasteur Institute." Monod sees the Pasteur Institute not only as a center of research and its application, but also as a test case, itself an experiment in research, with broad philosophic and social implications. He says:

"The beauty of the Institute is that it is a socialist institution, in the sense that it is a non-profit-making private foundation. Every cent from the industry will be transferred directly to research. And unlike a capitalist organization, it will not be transferred strictly or exclusively or even mainly to research designed to make new products developed for their sales value. That we do not do, and will never do. If we can survive in such a highly capitalistic, competitive society as that in France, we will have provided others with an example that such a thing can be done" (*New Scientist*, Dec. 7, 1972).

Obsolescence Catches Up

Even though the Pasteur Institute is a "nonprofit" institution, and pays no dividends for capital, it apparently has not been able to generate the funds essential for its bilateral mission, that is, basic research and teaching, on the one hand, and the manufacture and wide distribution and sale of medicinal products on the other.

A few years ago in an effort to improve the function of this dual mission, Monod set up a separate company for serum and vaccine manufacture, "The Pasteur Institute Production Ltd." Towards the same end, in 1962, a new factory was built at Louvier near Rouen at a cost of about 10 million dollars. Today the Institute urgently requires a modernization of its research facilities. Too much of its physical plant is outdated; too much of the equipment is obsolete and the quarters too tight. There have not been sufficient profits to enable the Pasteur Institute to *constantly* update its physical plant and there are no reserves available to construct a new center for its research and teaching activities. If the research and teaching sector of the Pasteur is to be brought up to date, new sources of capital would have to be tapped. Exploratory measures are being taken as to the feasibility of selling the historic thirteen acre site of the Institute itself on Paris' Left Bank and relocating at Gorches, a few miles west of Paris, in new quarters with facilities more appropriate to the 20th and 21st centuries.

Already Heading for Crisis in '61

The Institute was already heading for this crisis in 1961, the year which saw publication of some of the Institute's most epochal research, when Monod and his fellow-institute scientists published their work on messenger RNA and cellular control mechanisms—a major contribution to the foundation of modern molecular biology. For their achievements, Jacques Monod, François Jacob and André Lwoff were honored by the Nobel Committee. With growing recognition internationally and in France of their achievements, the scientists of the Institute were able to articulate their belief in the need for change at the Pasteur and their proposal for increased participation in the Institute's affairs by the scientists themselves was recognized in new by-laws introduced in 1967. In 1971, Nobel laureate Monod was drafted upon the urging of the Institute's leading scientists as the Institute director.

Monod then identified a new role for the Institute, that of pioneering what he considered a more socialist philosophy internationally at the Institute and a more participatory structure for the Institute's external relationship with society. Because of his concern with bureaucracy and in accord with Pasteur's own tradition, he shied away from "socialization" at the state level. He felt that the staff itself should be represented in management as also should representatives of government and the public, the latter by individuals who were completely independent.

With all its glorious tradition, its great staff and pioneering research and social ideals, the Pasteur Institute now faces a year of crisis—1975. Implicit in its trials are lessons for the future as they bear on nonprofit and profit oriented organizations engaged in biological health research and medicinal production the world over.

Industry's Research Efforts

The structure of these organizations vary. The Pasteur is not alone as a nonprofit institution. The Burroughs-Wellcome Foundation is the recipient of all the profits of Burroughs-Wellcome companies throughout the world. It differs from the Pasteur in that it has exercised its privilege in respect to patents and utilized the production of trademarks. Many of the private multinational companies in one respect are comparable to the Pasteur as they devote a growing percentage of their gross volume to research. As a result of their difference, that is, of their utilization of patent and trademark protection, their expenditure in research (at a time when the Institute was reducing its staff) has not resulted in budget deficits; they have been able to constantly modernize both their laboratory and production facilities and accumulate capital reserves for new centers of research and production. Thus, today, there are probably at least ten private pharmaceutical companies whose annual research budgets are multiples of that of the Pasteur Institute. While providing a profit for stockholders, these organizations have transferred ever-increasing sums directly to research. They may even be funding basic research with as much money as does the Pasteur itself.

These realities have not been lost upon some of the Pasteur's dedicated scientists and may be reflected in the director's goal to break new ground in regard to policies of the Institute—its discoveries are now to be patented to assure the generation of essential capital for operations, modernization of plant facilities and fiscal reserves from royalties and income.

Let us hope that, even in its vicissitudes, the Pasteur Institute will continue its contributions to the world of Science and the health of man.

Joy in Spearville as Doctor Strikes Out on Own

Dr. Guilherme Mobunda, a native of Mozambique who was an intern and resident in New York for eight years, has started to build a practice in Spearville, a town of 602 persons in an isolated area of western Kansas that has been without a physician for three years.

EPIGRAMS—Clinical and Otherwise

We doctors know
a hopeless case if—
listen: there's a
hell
of a good universe next door;
let's go.

Edward Estlin Cummings
(1894-1962)
One Times One

Medicine on Stamps

Vladimir Petrovich Filatov

Born in Mikhailovka, Russia, in 1875, the son of an ophthalmologist, he received his M.D. from the University of Moscow. He devised a successful procedure for corneal transplant that led to the development of "eye banks." He also devised many operations for restoration of eyelid deformities and introduced delayed pedicle flaps in autoplasties of the eyelids.

Text: Dr. Joseph Klar
Stamps: Mishkor Publications, Inc., New York

Vitamin D Analogues Ease Renal Osteodystrophy Pain

Medical Tribune Report

WINNIPEG, MAN.—Four patients with severe renal osteodystrophy had dramatic relief from bone pain after treatment with Vitamin D analogues 1,25 DHCC (1,25(OH)$_2$ Vitamin D$_3$) in two cases and 1 alpha OHCC (1 alpha Vitamin D$_3$) in two cases, it was reported here to the annual meeting of the Royal College of Physicians and Surgeons of Canada by Dr. Donald S. Silverberg, Associate Professor of Medicine, University of Alberta, Edmonton, Alta.

"To us it is a blessing because we've had nothing to treat these people with up to now," Dr. Silverberg told a press conference. "We don't know why they develop severe bone disease."

Treatment with 1,25 DHCC has extended up to one year, and with 1 alpha OHCC for up to 10 months.

Three of the patients belong to the same family, Dr. Silverberg said.

He welcomed the two Vitamin D analogues as useful additions to the treatment of renal osteodystrophy. It is too early to tell which of the two agents is superior, if indeed one is, he said.

X-Ray Evidence of Improvement

In one patient treated with 1,25 DHCC there is radiological evidence of improvement in hyperparathyroid and osteomalacid changes. In one treated with 1 alpha OHCC there was healing of fractures in the feet and improvement in bone mineral content as measured by photon absorptimetry. The mean serum calcium and phosphorus did not change in any subject, but the mean alkaline phosphintase was lower after treatment in one patient taking 1,25 DHCC and one taking 1 alpha OHCC Calcium balance was slightly negative in two patients prior to treatment with 1,25 DHCC but positive during trentment. Hypercalcemia occurred in the two patients taking 1,25 DHCC but responded rapidly to dose reduction.

Dr. Silverberg said the two vitamin D analogues will become more available in the next six to 12 months.

One patient treated with 1,25 DHCC had been confined to a wheel chair for a long time and within a short time was able to walk and now is walking long distances. There is bone healing and mineral content improvement.

"The change was so dramatic we have never seen anything like it," Dr. Silverberg said. One patient had shown no healing for four years but with a few months of 1 alpha OHCC, fractures healed and there was a rapid improvement in his pain within a week.

Co-authors were Dr. Kelvin R. Fletcher, Dr. M. R. Higgins, Dr. Thomas R. Overton and Dr. John B. Dossetor.

Psoriasis and Arthritis

► A study of 100 patients admitted to a general hospital dermatology service for control of resistant psoriasis showed a 32 per cent incidence of arthritis, in contrast to previous studies showing an incidence of only five to seven per cent, it was reported by Dr. Hugh Little, Sunnybrook Medical Centre, Toronto.

A total of 24 per cent of the study group had clinical findings (peripheral arthritis the most common) while a further 8 per cent had asymptomatic radiologic changes of the sacro-iliac joints. The patients with arthritis had significantly more psoriasis than those without arthritis ($p<.0005$). There was a positive correlation between the presence of arthritis and the severity of the skin disease, Dr. Little said.

Co-authors were Dr. R. S. Lester and J. N. Harvie.

infection control today

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Is it therapeutically safe for gram-negative pneumonia to be low-man on your diagnostic totem pole?

Tonsillitis is not like it used to be—but what exactly should the physician now do about it?

These stories, and others, appear in next week's *Infection Control Today*—it is published exclusively in Medical Tribune. Look for it!

NRC Board Backs Substitution Option For Pharmacists

Medical Tribune Report

WASHINGTON—Physicians would be required to give pharmacists, or explicitly withhold, the option of substituting one brand of drug for another, if a resolution of the National Research Council's Drug Research Board (D.R.B.) becomes law.

At present, the "substitution option"—usually exercised by the pharmacist to replace a brand-name drug with a less expensive equivalent—is allowed in only two states, Florida and Michigan. In all others, the pharmacist must first check with the prescribing physician.

The D.R.B.'s resolution represents an about-face for the board, charged with advising the Food and Drug Administration.

In 1973, it had considered strongly endorsing existing antisubstitution laws, on the ground that they protected the patient against inferior products.

After meeting with representatives of the American Pharmaceutical Association, the D.R.B. decided, however, that "in the absence of data to the contrary, there is no inherent reason for choosing the more expensive drug product simply because of the familiarity of the physician or pharmacist with the brand name."

The recommended law would not deprive physicians of the prerogative of requiring a particular brand. Only if the prescription contains no such explicit order, could the pharmacist substitute a less costly brand at his discretion. This would serve the patient, the D.R.B. resolved, by "providing the best product for the lowest cost."

The resolution was passed unanimously, with Dr. J. Richard Crout, director, Bureau of Drugs, F.D.A., abstaining. The F.D.A. has not taken an official stand on the issue.

Immunoglobulin Suppression Linked to High T Cell Activity

Medical Tribune Report

BETHESDA, MD.—Excessive activity of regulatory T cells has been implicated in the suppression of immunoglobulin synthesis in patients with common variable hypogammaglobulinemia (CVH), a heterogeneous group of disorders with increased incidence of infections, according to Dr. Thomas A. Waldmann, Chief, Metabolism Branch, National Cancer Institute.

Studies conducted by Dr. Waldmann and his colleagues suggest that the failure of B-lymphocytes to differentiate into antibody-producing cells in a large subgroup of patients with primary immunodeficiency is caused by circulating regulatory cells acting abnormally in an as yet unknown manner to suppress B-cell maturation. It had previously been thought that this failure was generally due to some intrinsic defect in the B-cells or a deficiency in extrinsic factors that facilitate B cells maturation.

Looking for a Drug

"CVH is the first disease associated with excessive suppressor cells," Dr. Waldmann told MEDICAL TRIBUNE. "Although we have only been working in tissue culture so far, what is quite exciting is the possibility of clinical applications. We are now looking for a drug that would put the brakes on these rampant T-cells without toxic side-effects."

In the investigators' experiments, normal B-lymphocytes were cultured alone in vitro and their quantitative production of immunoglobulins was noted in the presence or absence of the stimulating pokeweed nitrogen. Purified T-lymphocytes from patients with CVH were then co-cultured with normal lymphocytes from control patients. Under these conditions the normal cells failed to produce immunoglobulins even in the presence of pokeweed nitrogen.

A series of control studies by radioimmunoassay determined that the failure of immunoglobulin synthesis by normal cells in the presence of T cells from patients with CVH was not due to humoral factors. Nor did co-culture of cells from unrelated normal individuals result in significant inhibition of immunoglobulin synthesis.

Although Dr. Waldmann does not rule out the possibility that in some CVH patients the abnormality of the T-cell regulatory system is only a secondary effect of the disease, he believes that in the majority of cases it represents the primary defect.

Patronize Pharmacies, Japanese Public Urged

Medical Tribune World Service

TOKYO—The Japanese Health and Welfare Ministry hopes to convince the public that it would be better served if pharmacology were separated from medical practice.

Ninety nine per cent of doctors in Japan, the *Japan Times* reports, dispense the drugs that they prescribe. And according to a poll conducted in 1973, 75 per cent of the Japanese like it that way.

In the opinion of the Ministry, however, this system has led to abuses. Doctors are said to be writing many prescriptions for large amounts of drugs in order to make a profit.

To substantiate this charge, Ministry spokesman say that after a fivefold increase last October in the fee paid to the prescribing physician under the national insurance scheme, the number of prescriptions written increased by 50 per cent.

The Ministry will begin a campaign in April to change the public's mind. In particular, it will try to show that purchase of drugs at pharmacies would relieve doctors of paperwork and result in better and cheaper medical care.

Nutrition Computer at University of Wisconsin

A new weight-watcher at the University of Wisconsin is a computer that analyzes a person's diet and eating habits and makes recommendations for better nutrition. Shown here working with the machine are Prof. Nancy Johnson (right) and an assistant, Judy Bobinski.

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*Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: For use to relieve pain, in "conditions in which combined sedative and analgesic action is desired, such as, nervous tension and sleeplessness associated with pain or headache." Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivity to any of the components.

Precautions: Due to presence of barbiturate, may be habit forming. Excessive or prolonged use should be avoided.

Side Effects: In rare instances, drowsiness, nausea, constipation, dizziness, and skin rash may occur.

Adult Dosage: One to two tablets or capsules, repeated if necessary up to 6 per day, or as directed by physician.

Before prescribing, see package insert for full product information.

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Clofibrate, Niacin Fail Life-Prolongation Test

By ALAN FITZGIBBON
Special Tribune Correspondent

BETHESDA, MD.—Clofibrate and niacin have proved ineffective in prolonging the lives of male myocardial infarction patients, a panel of coronary heart disease specialists reported at a press conference here.

In a large-scale study to see whether the drugs would prevent recurrent heart attack, clofibrate-treated patients experienced a 20.0 per cent five-year mortality versus 20.9 per cent for control patients on placebo, and niacin-treated patients had a 21.2 per cent five-year mortality versus 20.9 per cent for controls.

The negative results produced by the 13-year, $40,000,000 Coronary Drug Project have led to the recommendation that clofibrate be dropped in treating CHD patients and a statement that niacin "may be slightly beneficial in protecting persons to some degree against recurrent nonfatal myocardial infarction."

Unanswered Question

The seven panelists at the press conference, which was sponsored by the National Heart and Lung Institute, emphasized that the study did not reveal whether clofibrate and niacin would be useful in preventing initial myocardial infarction in persons with high serum cholesterol levels. Dr. Robert I. Levy, director of N.H.L.I.'s division of heart and vascular diseases, said that question would have to remain unanswered for the time being because a clinical trial to resolve it would be beyond the institute's present budget.

Despite the finding that clofibrate and niacin do not significantly affect the five-year mortality of men who suffer heart attacks, the Coronary Drug Project produced much valuable information, said Dr. Jeremiah Stamler, the project steering committee's chairman and Professor of Community Health and Preventive Medicine at the Northwestern University School of Medicine.

Aside from demonstrating that the two drugs were useless for that specific purpose, the project showed that a clinical trial embracing more than 50 institutions and 8,000 patients is feasible and revealed much about the natural history of myocardial infarction, he said.

For example, it was found that mortality following heart attack may be predicted on the basis of 11 clinical or electrocardiographic variables: ST depression, cardiomegaly, New York Heart Association Functional Class, ventricular conduction defects, use of diuretics, intermittent claudication, serum cholesterol levels, arrhythmia, cigarette smoking, physical inactivity, and Q/QS electrocardiographic abnormality.

The Coronary Drug Project began in 1961 at the initiative of the National Advisory Heart Council, which noted the significance of CHD as a national health problem, the strong association between elevated serum cholesterol and increased CHD risk, and the availability of various drugs to reduce blood lipid levels. It was hypothesized that the serum lipids which may contribute to an initial infarction might to the same extent increase the threat of recurrent heart attack among survivors, and that lipid-lowering agents might counter that effect.

The project's clinical phase started in April 1965 at the first four participating clinics. Thirty-two clinics were added in 1966 and 19 the following year, bringing the total to 55, though two institutions dropped out before the project ended.

Patients enrolled in the project were men aged 30 through 64 who had suffered one or more myocardial infarctions categorized as class I or II by the New York Heart Association standard at least three months previously, who were free of specific diseases and conditions, and who showed no recent worsening of their CHD or had other major illnesses.

6 Treatment Groups

All patients were randomly assigned to one of six double-blind treatment groups: conjugated estrogens, 2.5 or 5.0 mg./day; dextrothyroxine sodium (Choloxin), 6.0 mg./day; clofibrate, 1.8 g./day; niacin, 3.0 g./day, and a lactose placebo, 3.8 g./day. Estrogen lowers serum cholesterol; the other active agents lower triglycerides as well.

The total number of patients enrolled was 8,341, of whom 1,101 to 1,119 were assigned to each of the drug groups and 2,789 to the control group.

Three of the regimens were dropped before the study ended when it became apparent that they were of no positive value. The first to go was estrogen 5 mg./day, which was discontinued in 1970 because it was not improving survival rates and patients in the regimen were experiencing more nonfatal cardiovascular events than controls. Dextrothyroxine was dropped in late 1971 because of decreased survival rates, particularly among higher risk patients. Estrogen 2.5 mg./day was discontinued in 1973, largely because of evidence that it increased the risk of thromboembolism without any compensatory improvement in survival rates.

Clofibrate and niacin were continued throughout the project's scheduled life, and the tentatively final data reported at the press conference were those received at the project's coordinating center through September of last year. The follow-up period for patients in these two drug groups was five years, though more than half were followed six years or more.

Side Effects From Both

Clofibrate and niacin did produce modest five-year reductions in serum cholesterol in the patients (6.5 and 9.9 per cent, respectively) and more marked reductions in triglycerides (22.3 and 26.1 per cent, respectively), but both drugs produced side effects.

Among the clofibrate-treated patients there was a statistically significant excess incidence of thromboembolism, angina pectoris, intermittent claudication, and cardiac arrhythmia, as well as an excess incidence of the endpoint of any definite or suspected nonfatal cardiovascular event when compared with the control group.

The niacin-treated group experienced a significantly lower five-year rate statistically of confirmed nonfatal myocardial infarction than the control group (8.9 versus 12.2 per cent, respectively), less angina pectoris, and fewer intermittent cerebral ischemic attacks. But because niacin was associated with an excess incidence of arrhythmias, gastrointestinal problems, and abnormal chemistry findings, the project's leaders urged that "great care and caution must be exercised if this drug is to be used" in CHD patients.

Besides Drs. Levy and Stamler, the press conference panelists were Robert L. Ringler, Ph.D., N.H.L.I.'s acting director; Dr. Kenneth G. Berge, Associate Professor of Clinical Medicine, Mayo Graduate School of Medicine; Dr. Christian R. Klimt, Professor of Social and Preventive Medicine, University of Maryland School of Medicine, and Dr. William J. Zukel, of N.H.L.I.

Heaf-Gun BCG Reaction

An Australian child shows the reaction to BCG administered from the multineedle Heaf gun in a nationwide experiment in the treatment of leukemia, conducted by the Royal Children's Hospital, Melbourne. A test treatment showed that a remission rate exceeding 50 per cent may be expected. The project will extend research undertaken in the late 1960s by Dr. George Mathe of France using the Heaf gun instead of scarifying for vaccine administration.

after taking a potent analgesic 360 times in

how big a dose will now bring relief if it is a narcotic?

"Tolerance is an ever-present hazard to continued use of narcotics. . . . The very first dose diminishes the effects of subsequent doses."[1] And, as increasing amounts of narcotics are required to control pain, distressing adverse effects—lethargy, hypotension, constipation, etc.—can needlessly debilitate the patient.

1. Sadove, M. S.: A look at narcotic and non-narcotic analgesics, *Postgrad. Med.* 49:182, June 1971.

how big a dose will now bring relief if it is Talwin®?

Chances are, the same 50 mg. Talwin Tablet you prescribe originally will continue to provide good pain relief. Talwin can be compared to codeine in analgesic efficacy: one 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. However, patients receiving Talwin Tablets for prolonged periods face fewer of the consequences you've come to expect with narcotics. There should be fewer "adverse effects" on her way of life.

Tolerance rare: Tolerance to the analgesic effect of Talwin Tablets is rare.

Dependence rare: *During three years of wide clinical use, there have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.*

*In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.**

Generally well tolerated by most patients*: Infrequently causes decrease in blood pressure or tachycardia; rarely causes respiratory depression or urinary retention; seldom causes diarrhea or constipation. Acute, transient CNS effects, described in product information, have occurred in rare instances following the use of Talwin Tablets. If dizziness, lightheadedness, nausea, or vomiting is encountered, these effects may decrease or disappear after the first few doses.

*See important product information for adverse reactions, patient selection, prescribing and precautionary recommendations.

in chronic pain
of moderate to severe intensity

Talwin® 50 mg. Tablets
brand of
pentazocine
(as hydrochloride)

Talwin® Tablets brand of pentazocine (as hydrochloride)
Analgesic for Oral Use—

Indication: For the relief of moderate to severe pain.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.*

In *prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the* drug *in anticipation of pain rather than for the relief of pain.*

Head Injury and *Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* Although respiratory depression has rarely been reported after oral administration of Talwin, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Decreased metabolism of the drug by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations (see *Acute CNS Manifestations* under WARNINGS); and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, toxic epidermal necrolysis.

Dosage and Administration: *Adults.* The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg.

When antiinflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with Talwin.

Children Under 12 Years of Age. Since clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

Duration of Therapy. Patients with chronic pain who have received Talwin orally for prolonged periods have not experienced withdrawal symptoms even when administration was abruptly discontinued (see WARNINGS). No tolerance to the analgesic effect has been observed. Laboratory tests of blood and urine and of liver and kidney function have revealed no significant abnormalities after prolonged administration of Talwin.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: Tablets, peach color, scored. Each tablet contains Talwin (brand of pentazocine) as hydrochloride equivalent to 50 mg. base. Bottles of 100.

Winthrop Laboratories, New York, N.Y. 10016 Winthrop

Implants Pushed As an Alternative For Birth Control

Medical Tribune World Service

BUENOS AIRES—Recent technical refinements have brightened the outlook for implants of progestational agents as an alternative method of fertility control, Dr. Horacio B. Croxatto, a Chilean investigator told the Eighth World Congress of Fertility and Sterility.

The experience of 5,000 Latin-American women with this method has been highly favorable, said Dr. Croxatto, Professor of Physiology at the Laboratory of Endocrinology, Institute of Biological Sciences, Catholic University of Chile, Santiago.

No 365 Chances to Fail

Subdermal implants of Silastic or dimethicone capsules containing megestrol acetate (MA) give a woman contraception comparable with continued oral administration of pure progestogens, he said, and the technique possesses the special advantage that the patient is not given 365 opportunities a year to foil.

Excellent patient acceptability was reported by Latin-American populations in spite of the frequency of alterations of bleeding rhythm at the start of treatment.

Silastic capsules filled with progestational agents and Silastic cylinders impregnated with the agents with an outside diameter of 2.4 mm. can be inserted through a 13-gauge needle, Dr. Croxatto explained. They vary in length from 1 to 3 cm. Ten different progestogens have been used so far.

Capsules or rods are usually inserted under the skin of the forearm or in the gluteal region during the first days of the cycle. Local reaction is negligible, and there are rarely complications like infection or expulsion, Dr. Croxatto said.

The range of release of progestogens varies from 3 to 100 micrograms, cm./day, and rods give faster release than capsules. Norethindrone acetate has the highest rate of release and norgestrel the lowest.

Intermenstrual Bleeding

The most common side effect seen with progestogen implants has been intermenstrual bleeding. Megestrol acetate, D-norgestrel, and R 2010 produce intermenstrual bleeding in about 30 per cent of the cycles at the start of treatment, Dr. Croxatto said, but there is a steady decline of intermenstrual bleeding during the first year, a partial rebound when the implant is replaced, and again a declining trend through the year to a level below 5 per cent.

We know Librium works.
(chlordiazepoxide HCl)

We're still learning more about how and why.

Value of continuing animal research

Clinical knowledge of Librium is extensive, yet its mode of action remains under continuing study. Data from animal experiments have been presented here for their intrinsic interest and because such findings often provide direction to new research, both experimental and clinical. *However, conclusions from such studies may not always be extrapolated to humans.*

Is the limbic system the "Librium (chlordiazepoxide HCl) system"?

A great deal of experimentation on various animal species suggests that the limbic system is the principal site of action of Librium. Thus, in freely moving cats with electrodes implanted in the brain, Librium 5 mg/kg i.p. slowed electrical activity in the hippocampus, amygdala and septal areas but not in the neocortex which was significantly affected only at higher doses.[1,2] Current investigations on monkeys,[3,4] however, indicate that other subcortical structures may be implicated in the effect of Librium.

Other investigators, through electrophysiologic studies[5] in intact, conscious cats and monkeys, have demonstrated that chlordiazepoxide activates structures involved in the rewarding system—the preoptic area, lateral hypothalamus, septal region and hippocampal formation. At the same time, it appears to *inhibit* structures implicated in aversive behavior—the thalamic nuclei of the diencephalon and the midbrain reticular formation (MRF).

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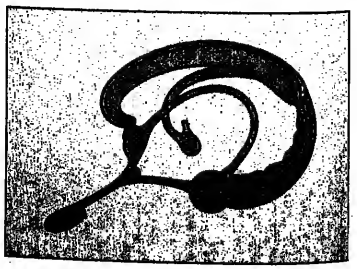
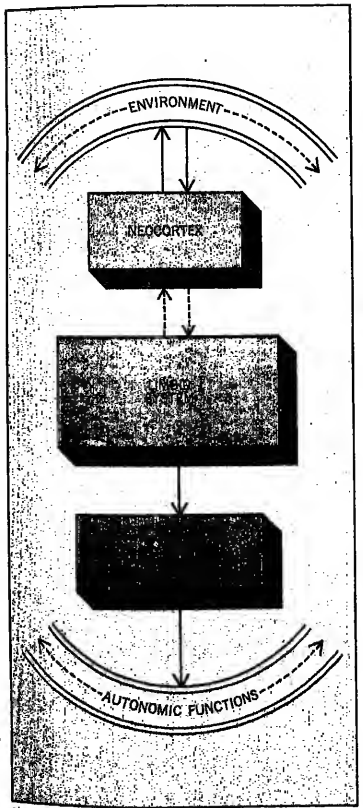




Schema demonstrating hypothetical pathways of emotional activity and its related expression in laboratory animals.

Clinical significance of excessive anxiety

Anxiety, when inappropriate and immoderate, may not only have adverse psychologic effects but may also cause various somatic disturbances. Reduction of excessive anxiety thus contributes to relief of anxiety-linked emotional and physical disorders.

Antianxiety action of Librium (chlordiazepoxide HCl)

The dependable action of Librium has been demonstrated in the relief of excessive anxiety and tension occurring alone or in association with functional and organic disorders—usually without adversely affecting performance. Librium is often used concomitantly, when anxiety is a contributing or complicating factor, with certain specific medications of other classes of drugs, *e.g.*, cardiac glycosides, diuretics and antihypertensives.

Adjunctive use of Librium is recommended when counseling, reassurance or other nonpharmacologic measures alone are not considered sufficiently effective. When anxiety has been reduced to manageable levels, therapy with Librium should be discontinued.

Librium®
(chlordiazepoxide HCl)
5 mg, 10 mg, 25 mg capsules

ROCHE

We're still learning more about it to make it more useful to you.

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or overpodatio., increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

ROCHE Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Tribune Economic Analysis

Car Dealers Balk At Taking Plants' Overproduction

By Eliot Janeway
Consulting Economist

For the first time in the history of the automobile business, this slump has been forcing dealers to refuse to absorb more overproduction from factories. Consequently, the factories are competing with their own dealers to see whose inventory-carrying burdens are worked off first. But there's no shortcut back to health for the automobile business while the dealers remain sick.

The splash made by the rebate offers is ballyhooed as plausible proof of the normal recovery Washington has been seeing around the corner. The factories that were realistic enough to start the rebates know better. They are realistic enough to recognize that raising cash this way will not correct the auto glut. The rebates will only accelerate sales that would otherwise not have been made until next summer in view of this winter's statistics.

Another RFC?

Trial balloons publicizing the uses and need of another Reconstruction Finance Corporation have been in vogue ever since the auto business went bad and revived Detroit's memory of old bankruptcies.

The RFC helped speed up the country's workout from the last Depression. Its first salvage job was that of banking the busted banks. This gave it plenty to do. It continued to take on new jobs as the government's banker of last resort—first in mobilizing government-salvage operations, like railroads, and then in financing wartime expansion. However, history never repeats itself in quite the same way.

As a matter of practical politics in an economic emergency, the project to launch an RFC to bail out large manufacturers in wobbly condition would not stop there. Like it or not, no new RFC for busted factories would carry them unless it carried their dealers, too. The "main drag" showrooms of the country's dealers is where the American economy's arteries are clogged.

2 Chief Rabbis Disagree On Oral Contraceptives

Medical Tribune World Service

JERUSALEM—Chief Rabbi Shlomo Goren, spiritual head of the Ashkenazi community, has endorsed the use of oral contraceptives by Jewish women if they have fulfilled the Biblical command to "be fruitful and multiply"—that is, if they have had at least one son and one daughter. The husband, however, would have to agree, he added.

Chief Rabbi Ovadia Yosef of the Sephardic community rejected this position. A woman might take the "pill" only to prevent a birth that would endanger her life, he said.

d-Fetoprotein Data Complement Placental Lactogen

Medical Tribune World Service

BUENOS AIRES—Human placental lactogen (HPL) appeared to be a better indicator of fetal viability in threatened abortion than alpha-fetoprotein (AFP) in Finnish studies reported here.

Both determinations should be made, however, the investigators told the Eighth World Congress on Fertility and Sterility.

Drs. Leena Gsroff and Markku Seppala, of the Central Hospital, University of Helsinki, said that HPL and AFP were measured prospectively by radio-immunoassay in 112 women with vaginal bleeding during the first or second trimester.

HPL was considered abnormally low when below the 2.5th percentile and AFP abnormally high when above the 97.5th percentile.

Pregnancy continued beyond 28 weeks in 43 cases, and 69 patients aborted spontaneously.

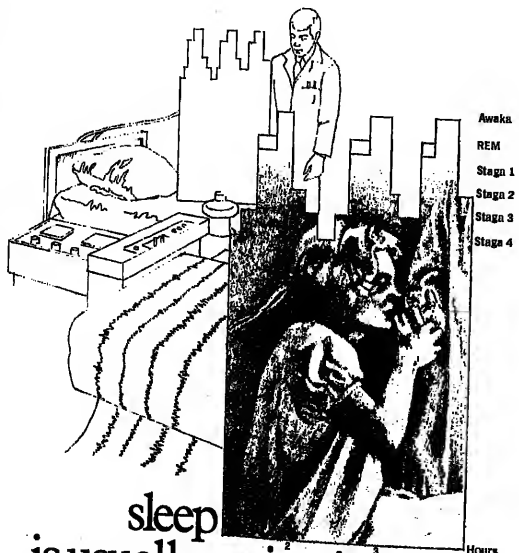
In the aborted cases after 10 weeks' gestation, 38 out of 56, or 62 per cent of the women, had either a low or borderline HPL level, while only five out of 69, or 7 per cent of all women who aborted, had a high or borderline AFP concentration.

Information Complementary

The diagnostic information given by both AFP and HPL levels was found necessary because a normal HPL level was found in all five cases with raised maternal AFP. And the AFP level was normal in 35 out of the 36 women with low HPL.

Four out of five patients with an unequivocally elevated AFP level aborted. The remaining case was that of a twin pregnancy in which one fetus had died. Two cases with borderline AFP levels were also associated with fetal death. The different information given by the two markers may be explained by their different sites of origin, Dr. Garoff said. While HPL is synthesized by the syncytiotrophoblast, the evidence presently available suggest that maternal AFP is of fetal origin.

Drs. Garoff and Seppala are in the Department of Serology and Bacteriology and the Department of Obstetrics and Gynecology, University Central Hospital, Helsinki, Finland.

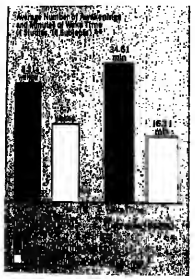


sleep is usually maintained with fewer nighttime awakenings...
a consistent benefit of
Dalmane (flurazepam HCl) proved by a 17-night clinical study in the sleep research laboratory evaluating effectiveness in insomnia patients[1]

Eight patients received no medication on nights 1-4; Dalmane (flurazepam HCl) or placebo on nights 5-9; crossover capsule, nights 10-14; and no medication, nights 15-17. While placebo had no significant effect on sleep maintenance, Dalmane reduced nighttime awakenings by 55.1% when given on nights 5-9, 43.7% on nights 10-14. When four control subjects received placebo on the 10 "drug" nights, awakenings *increased* 11.5% over baseline.[1]

Clinical Trials

by Oldden



confirmed by clinical studies in four geographically separated sleep research laboratories[2-5]

Using a 14-night protocol, involving eight insomniac and eight normal subjects, four studies confirmed the sleep-maintaining effectiveness of Dalmane (flurazepam HCl) and the reproducibility of this response. On average, one 30-mg capsule reduced number of awakenings by 31.3% and wake time by 52.6%. In all these studies, Dalmane induced sleep rapidly, on average within 17 minutes; reduced nighttime awakenings; and provided, on average, 7 to 8 hours of sleep without repeating dosage.[2-5]

Dalmane (flurazepam HCl) induces and maintains sleep, with relative safety

Dalmane is generally well tolerated; morning "hung-over" has been relatively infrequent. While dizziness, drowsiness, lightheadedness and the like have been noted most often, particularly in the elderly and debilitated, physicians should be aware of the possibility of more serious reactions, as noted in the Complete Product Information.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, direct bilirubins and alkaline phosphatase. Paradoxical reactions, e.g., excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults*, 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

when restful sleep is indicated
Dalmane (flurazepam HCl)

One 30-mg capsule h.s. – usual adult dosage (15 mg may suffice in some patients).
One 15-mg capsule h.s. – initial dosage for elderly or debilitated patients

- induces sleep within 17 minutes, on average
- reduces nighttime awakenings
- sustains sleep 7 to 8 hours, on average, without repeating dosage

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5. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Pyridoxine Aids Some 'Pill' Users With Depression

Medical Tribune World Service

MEXICO CITY—Depression associated with estrogeo-progestogen oral contraceptives occurs in a significant group of women and can be successfully treated in some of them, the Fourth International Congress on Hormonal Steroids was told here.

"Although it has been suggested that oral-contraceptive-induced depression may be a psychological phenomenon and that it is most likely to develop in women with a history of a previous depressive illness or severe premenstrual tension, the effects of metabolic changes induced by oral contraceptives should not be ignored," cautioned Dr. P. W. Adams, of St. Mary's Hospital Medical School, University of London, England.

Biochemical Rationale

He gave this biochemical rationale: Amine metabolism is altered in depression. The contraceptive pill is known to affect tryptophan metabolism. Tryptophan is a precursor of two of the brain amines implicated in depression.

Dr. Adams reported on results of a placebo-controlled crossover study on the effects of pyridoxine upon depression associated with the use of oral contraception. Thirty-nine women with no previous history of severe premenstrual tension or psychiatric illness were studied. Nineteen had vitamin B_6 deficiency. There was no difference between the deficient and nondeficient women with respect to age, dietary intake of B_6 and protein, or duration and nature of oral contraceptive medication.

The conclusion drawn from the study was that in a significant number of women with true B_6 deficiency, the depression can be corrected simply with pharmacologic doses of the vitamin. Depression in this group was thought to be due to the changes in tryptophan metabolism resulting in impaired 5-hydroxytryptophan decarboxylase activity in the brain.

In the remainder of the women, the metabolic basis of the depression induced by oral contraception was said to be less clearly established but possibly caused by deficiency of substrate in the brain for amine synthesis.